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AN ECONOMIC EVALUATION OF NABUMETONE/RELIFEX COMPARED WITH IBUPROFEN AND A WEIGHTED NSAID COMBINATION

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THIS PAPER REPORTS WORK IN PROGRESS

AND MUST NOT BE QUOTED WITHOUT THE

AUTHORS PERMISSION

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ABSTRACT

An Economic evaluation of Nabumetone/Relifex compared with Ibuprofen and a weighted NSAID combination.

Objective: An economic evaluation of *Nabumetone/Relifex*[*] compared with alternative NSAIDs[#], in patients with Osteoarthritis (OA) or Rheumatoid Arthritis (RA), using the technique of clinical decision analysis to model costs and outcomes, building on the results of a large open label US clinical study, from a National Health Service (NHS) perspective.

Methods: Three decision analytic models of the use of NSAIDs in the treatment of OA/RA and the management of associated major and minor side effects were constructed. Each model was used to identify the difference in morbidity; perforations, ulcers and bleeds, and associated mortality for a cohort of 20,000 patients prescribed Nabumetone compared to a cohort of 20,000 patients prescribed either Ibuprofen or a Weighted NSAID comparator. The life years gained were calculated using the life table method. The differences in outcome were related to the differences in cost. All costs and benefits of treatment were discounted at 6% per annum. Sensitivity analysis was undertaken to test the robustness of the results to changes in the risk of both minor and major side effects.

Results: In the treatment of OA/RA, Nabumetone carries a lower risk of major side effects than either Ibuprofen or the Weighted NSAID comparator. As a direct result, mortality in the cohort treated with Nabumetone is lower. The additional cost incurred to avoid these deaths ranges from £32,706 to £60,968, depending upon the assumptions made about clinical management of side effects. The cost per life year gained ranges from £1,656 to £3,087.

Conclusion: In the treatment of OA/RA Nabumetone is as effective as alternative NSAIDs with the advantage of a lower risk of major side effects. If reducing the risk of major side effects is a priority then the additonal potential costs of prescribing Nabuemtone to achieve this end compares favourably to many expenditures already made within the NHS. On this basis use of Nabumetone may be considered a cost effective use of resources from a health service perspective.

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[*] Relifex is a trade mark of SmthKline Beecham

[#] Plain NSAIDs only i.e. excludes combinations

PURPOSE OF PAPER

The purpose of this paper is to report an economic evaluation of *Nabumetone/Relifex*[*] compared with alternative Non-steroidal Anti-inflammatory Drugs (NSAIDs)[#], in patients with Osteoarthritis (OA) or Rheumatoid Arthritis (RA), using the technique of clinical decision analysis to model costs and outcomes, building on the results of a large, open-label, randomised controlled, multi-centre, US clinical study, (known as the NAB101 study)[1], to reflect a UK Health Service perspective.

BACKGROUND

There are more than twenty Non-steroidal Anti-inflammatory Drugs (NSAIDs) listed in the British National Formulary [2] and it has been calculated that these account for 5 per cent of all NHS prescriptions[3] .The effectiveness of specific NSAIDs is difficult to predict and may be dependent upon the characteristics of the individual patient. Side effects are common and can occasionally be life threatening.[2]

Common minor side effects includes dyspepsia, flatulence and diarrhoea. The most common major side effects related to NSAID use are gastric ulcers and bleeds. Generalisable estimates of the risk of side effects associated with individual NSAIDs are difficult to find. Problems encountered with published data include unrealistic dosage, atypical study populations, non-representative study design, and inappropriate comparators.

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[*] Relifex is a trade mark of SmthKline Beecham
[#] Plain NSAIDs only i.e. excludes combinations

DESCRIPTION OF THE CLINICAL (NAB101) STUDY

The NAB101study[1] avoids many of the pitfalls detailed above, taking a naturalistic approach to dosing, study population, design and comparators. The NAB101 study was a large (over 4000 patients enrolled) open-label, randomised controlled multi-centre trial comparing five NSAIDs on the basis of safety and efficacy in the treatment of Osteoarthritis and Rheumatoid Arthritis.

All patients entered into the trial were randomised to receive one of five NSAIDs, Nabumetone (n=3,315); Diclofenac (n=296); Ibuprofen (n=235); Piroxicam (n=286); or Naproxen (n=279). No washout phase preceded randomisation. Patients were treated for 12 weeks (or until withdrawal). Dosage commenced at the lowest level and was increased, if needed, after two weeks. The dosage ranges were; Nabumetone 1000 to 2000mg/day; Diclofenac 100 to 200mg/day; Ibuprofen 1200 to 3200mg/day; Piroxicam 10 to 20mg/day; and Naproxen 500 to 1000mg/day for OA patients or 1500mg/day for RA patients.

Disease modifying antirheumatic drugs or prednisone were permitted if therapy had started three or more months previously and dosage had been stabilised. Patients were excluded if they had any of the following conditions: history of liver disease or blood dyscrasia, uncontrolled hypertension, abnormal laboratory values, recent myocardial infarction, uncompensated congestive heart failure, or functional class IV arthritis.

Patients were also excluded if they were pregnant or lactating, not practising contraception, had an active gastrointestinal bleed or peptic ulcer within 1 month, had a hypersensitivity reaction to Aspirin or NSAIDs, had recently used

investigational drugs, or needed coumarin, anticonvulsants, hydantoins or more than 1 NSAID.

Safety assessments were performed at baseline, four weeks and 12 weeks. Occurrence of any adverse events was identified and recorded by the investigator. Each adverse event was recorded only once, even if it occurred more frequently. Attribution to study medication and outcome were also recorded. Severe adverse events lead to automatic withdrawal from the study, otherwise withdrawal was at the discretion of the investigator. Perforations, ulcers and bleeds (PUBs) required further clinical investigation, treatment and or hospitalisation. Within the study, PUBs were not identified by endoscopy screening, but were diagnosed and then screened.[1]

The use of non-placebo comparators, randomisation and large sample size combined, make the NAB101 study one of the best available sources of data on safety and efficacy for the five NSAIDs included in the study: Nabumetone, Diclofenac, Ibuprofen, Piroxicam, and Naproxen. The study demonstrated that all of the NSAIDs considered were clinically effective. There were, however, differences in the major and minor side effect profiles.

METHODS

The costs and benefits of using Nabumetone, Ibuprofen and a representative combination of alternative NSAIDs proportionately weighted to represent their respective level of prescribed use in the UK (Naproxen, Piroxicam, Ibuprofen and Diclofenac)* , subsequently referred to in the text as 'a Weighted NSAID Combination', were quantified using Clinical Decision Analysis Techniques.[4] This consists of identifying the treatment paths that a patient can follow from the initial choice of NSAID, through to the management of major and minor side effects, on to the end of the treatment episode.

There are a number of stages involved in the construction of a clinical decision analytic model. The first stage involves the description of all possible aspects of the treatment from initial prescription through to the termination of treatment (for whatever reason). This is most easily thought of as constructing a flow chart which starts with the initial choice of treatment, identifies all points in the process where a change in treatment might occur, and covers all possible treatment termination options.

Once the flow chart has been constructed, information has to be attached at points where the treatment can change. These are referred to as nodes, and may be either *chance nodes*, in which case the *probability* of the treatment changing in any particular way has to be identified; or *decision nodes*, in which case the *decision rule* determining whether treatment changes in any particular way has to be identified. In this study, the choice of NSAID is a decision node; whether a patient will experience a minor or major side effect is a chance node.

* Plain NSAIDs only i.e. excludes combinations

The decision rules for this study were determined in consultation with clinicians who have significant experience of treating OA/RA with NSAIDs. The probabilities for the chance nodes, relating to the possible occurrence of minor or major side effects were taken from observed outcomes in the NAB101 study[1] (See Table 1)

For an economic evaluation, a further stage requires the identification, measurement and valuation of the costs associated with each outcome from each decision or chance node. In this case these were the cost of each NSAID in the study, the cost of treating major side effects and the cost of treating minor side effects.

Table 1: Risk of Minor and Major Side Effects by NSAID (Probabilities used in Chance Nodes of Decision Trees)

Side Effect	Nabumetone	Ibuprofen	Naproxen	Piroxicam	Diclofenac
Abdominal Pain	0.043	0.068	0.057	0.045	0.088*
Abnormal Hep. Function	0.005	0.0	0.0	0.004	0.037†
Arthralgia	0.006	0.009	0.007	0.01	0.003
Constipation	0.017	0.009	0.011	0.01	0.017
Diarrhoea	0.07‡	0.009	0.025	0.021	0.054
Dizziness	0.009	0.017	0.007	0.007	0.014
Dyspepsia	0.066	0.043	0.122ξ	0.084	0.084
Oedema	0.017	0.03	0.025	0.01	0.014
Flatulence	0.028	0.017	0.014	0.031	0.014
Gastritis	0.004	0.013	0.0	0.004	0.017‖
Headache	0.024	0.013	0.014	0.007	0.027
Nausea	0.04	0.043	0.054	0.031	0.041
Rash	0.013	0.009	0.007	0.007	0.014
Vomiting	0.005	0.004	0.011	0.014	0.003
Perforations, Ulcers and Bleeds (P.U.B.s)	0.0003	0.009§	0.007§	0.003	0.003

Compiled from Tables 2 and 4 in Eversmeyer et al:[1] Each figure is the decimal presentation of a percentage risk, thus 0.043 equals 4.3% . If one thousand people received Nabumetone,43 would be expected to experience abdominal pain. *p<0.002 versus Nabumetone, †p<0.01 versus all other NSAIDs Combined, ‡p<0.003 versus Naproxen, Ibuprofen and Nabumetone, ξp<0.002 versus Nabumetone and Ibuprofen, ‖p<0.02 versus Nabumetone, § P<0.02 vs Nabumetone

DECISION TREES

Choices in the treatment of OA/RA using NSAIDs can be summarised as:

- Choice of initial NSAID; for the purposes of this analysis one of the five NSAIDs included in the NAB101 study.
- Choice of treatment of minor side effects; co-prescription, switch to alternative NSAID, or switch to an alternative NSAID as well as co-prescription.
- Choice of treatment for major side effects.
- Choice of treatment for OA/RA subsequent to a major side effect.

These choices rest with the clinician. An additional choice which rests with the individual patient is whether to withdraw from treatment. This choice can be exercised at any point in the treatment regime.

In order to simplify the analysis two models have been constructed, containing a subset of the choices outlined above. The first (figure 1) reflects the treatment protocol of the NAB101 study, the second (figure 2) is a simplification of recommended clinical practice described in the literature[2] and as described by the clinicians.

In each decision tree there is a potential option for self-withdrawal from treatment. Although it is known that non-compliance does occur with NSAIDs, it proved impossible to identify reliably the proportion of patients who would choose this path. Therefore, it was assumed that all NSAIDs would be equally affected by non-compliance and therefore that the comparison would remain unaffected.

"Within Study" Model Decision Tree

Figure 1 shows the decision tree based on treatment patterns within the NAB101 study. Patients are initiated on any one of five alternative NSAIDs, (Nabumetone, Piroxicam, Naproxen, Ibuprofen or Diclofenac), and treated for up to 12 weeks. Possible initial outcomes are efficacious treatment without side effects, efficacious treatment with a minor side effect, efficacious treatment with major side effects (i.e. Perforations, Ulcers and Bleeds - PUBs). Non-efficacious treatment has not been included as a possible outcome because the NAB101 study found that the NSAIDs included in the study were all effective in treating OA/RA at the population level, although for individuals any drug may be ineffective.[5]

Patients who experience no side effects receive no additional interventions during the three months of the model time horizon. Patients who experience minor side effects receive co-prescription for that side effect and continue to be prescribed the original NSAID for the 3 months. Patients who experience major side effects stop treatment with an NSAID and receive treatment for their major side effect.

"Rational Practice" Model Decision Tree

Figure 2 shows the decision tree developed to reflect clinical practice and rational treatment choices in the NHS recommended in the literature[2] and described by collaborating clinicians. Patients are initiated on one of five alternative NSAIDs, (Nabumetone, Piroxicam, Naproxen, Ibuprofen or Diclofenac). Possible initial outcomes are efficacious treatment without side effects, efficacious treatment with a minor side effect, efficacious treatment with major side effect. This is a simplification of the possible treatment pathways, with combinations of switching and co-prescribing being one example of treatment options not explicitly modelled.

Patients who experience no side effects receive no additional interventions during the three months of the model time horizon. Patients who experience minor side effects are switched from their initial NSAID to the NSAID with lowest risk of the side effect that they experienced, based on the results of the NAB101 study. For example, a patient being prescribed Ibuprofen who experienced headache would be switched to Piroxicam, as this has the lowest risk of headache amongst the four alternative NSAIDs (See Table 1). In the model switching takes place after four weeks. Patients who experience a major side effect stop treatment with NSAIDs and receive treatment for their major side effect.

Those patients who are switched, face a second set of outcomes. Patients who experience no side effects on the NSAID they are switched to remain on that NSAID for the remaining two months of the three month model time horizon. Patients who experience a minor side effect receive co-prescription for their minor side effect and remain on the NSAID to which they have been switched. Those patients who experience a major side effect on the NSAID to which they have been switched stop treatment with NSAIDs and receive treatment for their major side effect. Patients who experience a major side effect are then placed on maintenance therapy for gastric bleeds and face a risk of a repeat episode. Maintenance therapy is an additional intervention which helps to heal and protect the damaged tissue and thereby reduce the risk of future bleeding. Results for this model will be presented for the three month period of the NAB101 study, and separately for the three month treatment period plus the longer term effects of NSAID treatment i.e. rebleeds, maintenance therapy and the associated mortality; which are directly attributable to events during the three months of treatment. It has been assumed that NSAID related bleeds are no different from other bleeds, and therefore that the risk of a rebleed is independent of the continuance of NSAID therapy. Although anecdotal

evidence suggested that NSAID related bleeds may be different from other bleeds, no data was found in the literature to support this assumption.

Figure 1: Within Study Model Decision Tree

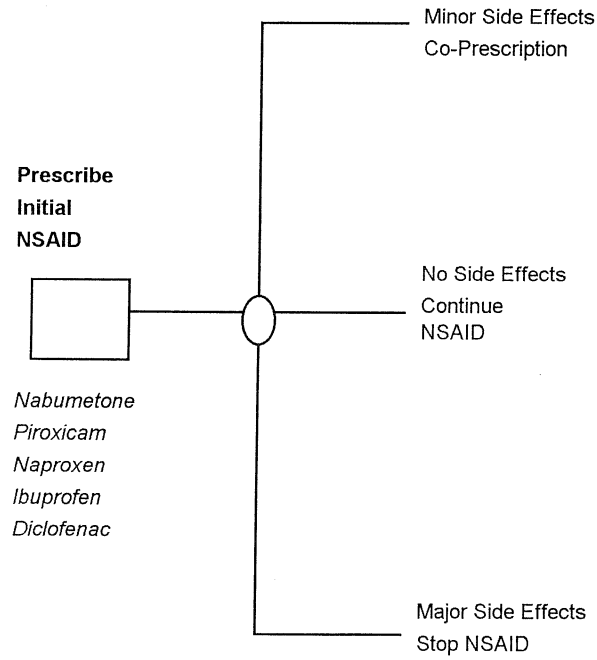
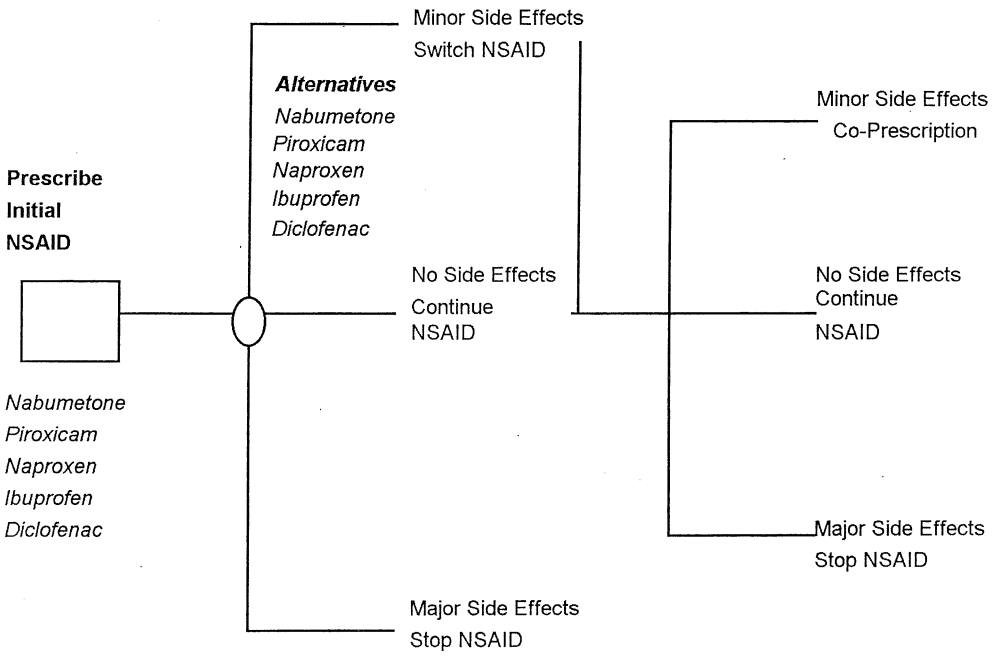


Figure 2: Rational Practice Model Decision Tree



CONSTRUCTING THE WEIGHTED NSAID COMBINATION

The weights used in constructing the NSAID combination were the UK market share for each NSAID. Ibuprofen is the market leader with 55.8% of the first line/initial use market share, followed by Diclofenac on 26.9%, Naproxen on 15% and Piroxicam with 2.3% of the market (The New and Change Therapy Enquiry Database - Compufile). These data were used in the Rational Practice model, where the first prescription determines the cumulative risk of each side effect. In the Within Study Model, the total market shares were used. Ibuprofen has 36.8% of the market, Diclofenac has 37.7% of the market, Naproxen is next with 18.5% of the market and Piroxicam has 7.5% of the market.(Mediplus Database - IMS). These four NSAIDs and Nabumetone represent 71% of the UK prescription market for NSAIDs used in OA/RA (Mediplus Database - IMS).

The use of the Weighted NSAID as a comparator involves combining data from the US study with UK market shares. Although the range of dosages approved for these NSAIDs is greater in the US than the UK, the actual dosages prescribed in the trial were almost all within the range approved for use in the UK. On this basis it was decided that combining these two datasets was acceptable.

COSTS

Four categories of cost had to be identified for the economic evaluation; the cost of three months treatment for each NSAID in the study, the cost of treating minor side effects, the cost of treating major side effects, and the cost of treating the longer term sequelae of major side effects.

The cost of three months treatment for each NSAID depended upon assumptions with regard to dosage. Three possible assumptions were identified: to use the dosages observed in the trial; to base cost on the dosage observed in current practice; or to use recommended dosages (based on manufacturers recommendations). It was decided to use the dosages observed in the trial on the basis that the outcomes observed in the trial are likely to be related to dosage and, therefore, consistency required that the within trial dosage was used in the model. The cost of a three month course of each NSAID was based on prices given in the Drug Tariff and the Chemist and Druggist Monthly Price List. (May 1995)

There were a number of options for costing major side effects. Experienced clinical opinion could have been sought to identify resource usage, which could be subsequently costed. Alternatively, the NAB101 study could have been used to identify the resources used, which could then form the basis of a costing exercise. Another option was to use published costs, specifically the extra-contractual referral (ECR) costs for a sample of NHS Trusts.

The first option was not chosen because the major side effects that experienced clinicians treat might be the more severe, and correspondingly expensive. Therefore, basing costing on their resource use might lead to an over estimate of the true

expected cost of treating a major side effect. The second option was not used because of the well documented divergence between UK and USA treatment practices and costs. Basing costs upon the NAB101 study might have lead to a significant over-estimate of the cost to the NHS of treating major side effects.

The third option, which was adopted was to use published ECR charges produced by NHS Hospital Trusts in Trent Region. These costs are legally required to be the true economic cost of the service in question. No subsidisation between procedures is allowed. As such, they should reflect the real resources used by the intervention and a formal costing study would be expected to produce the same results.

The ECRs for all types of gastric bleed were obtained for all Trusts in Trent Region. The sample covers the full range of hospitals from small District General Hospitals in rural areas to large Teaching Hospitals in urban centres, and was therefore felt to be representative. The distribution of activity across the range of gastric bleeds was obtained from a hospital activity database compiled by Trent Region. These two data sets were then combined to calculate the expected cost of a gastric bleed in Trent Region. The cost of ancillary services such as ambulance transport and out-patient clinics were added to this, as well as the cost of General Practitioner consultations pre-admission and post-discharge, to obtain the cost of a major side effect. The estimate that resulted from this process was passed to a number of gastroenterologists for confirmation that it represented a credible estimate of the cost of a gastric bleed.

A fourth and preferable option would have been to conduct an observational costing study of the treatment of PUBs. Whilst beyond the scope of the present study, this may form the basis of a further investigation.

The expected cost of a major side effect was calculated on the assumption that all major side effects were gastric bleeds, as was the case in the NAB101 study. The cost of treating each category of gastric bleed was taken from Trent Region Extra Contractual Referral prices for 1995/6. The distribution of bleeds across category was obtained from activity data held by Trent Regional Office. These data were combined to calculate the expected cost of a gastric bleed.

The range of minor side effects was such that incorporating individual costs for each minor side effect would have complicated the model without any expectation of impacting upon the results. Therefore the costs of treating minor side effects by co-prescription was assumed to be a nominal £20 for a GP consultation and prescription.*

If the minor side effect was treated by switching the cost of treatment for the remaining period was assumed to be the difference in cost for two months treatment on the original NSAID and two months treatment on the second NSAID.

Recommended maintenance therapy for the prevention of rebleeds is cotreatment with Histamine 2 Receptor Antagonists (H2RAs).[6] In actual practice other treatments such as misoprostil may be used. However, the model conforms to the recommendations of the Royal College of Physicians[6]. Data from the Mediplus Database (IMS) showed that Ranitidine was the most commonly co-prescribed H2 antagonist for the five NSAIDs in the NAB101 study. Although it is recommended that maintenance therapy continues for life after a gastric bleed, evidence on actual practice showed that the majority of people received maintenance therapy for a

* If treatment of minor side effects was given by a specialist rather than a GP, the cost would be considerably higher.

relatively short time, with only 30% being prescribed H2 antagonists for more than two years. Based on the observed data (personal communication Prof. C.F. Hawkey), maintenance therapy was assumed to last for 55 weeks.

All costs incurred in the future were discounted at 6% per annum (HM Treasury recommendation). It was assumed that rebleeds which occur would be distributed evenly over the five years post original bleed. In practice one might expect them to be skewed towards the earlier end of the period so this assumption might lead to a slight underestimate of the rebleed costs.

OUTCOMES

Four outcomes were calculated for each model:

- Total cost of treatment for a cohort of 20,000 patients initiated on each NSAID.
- Number of Major Side Effects (P.U.B.s) for a cohort of 20,000 patients initiated on each NSAID.
- Number of deaths for a cohort of 20,000 patients initiated on each NSAID.
- Number of minor side effects for a cohort of 20,000 patients initiated on each NSAID.

The NSAIDs were compared on five dimensions, in each model:

- Expected total cost of treatment per patient on each NSAID.
- Cost per Major Side Effect Avoided by using Nabumetone.
- Cost per life year gained (LYG) by using Nabumetone rather than comparator NSAID.
- Cost per death avoided by using Nabumetone rather than comparator NSAID.
- Net Incidence of minor side effects (i.e. The reduced or increased incidence of minor side effects avoided/or caused by using Nabumetone rather than a comparator NSAID).

The number of life years saved per death avoided was calculated from the age profile of the subjects who experienced major side effects in the NAB101 trial, combined with life expectancy tables for the UK population in 1990/92.[7] These data were used to estimate an average life expectancy for patients who experience major side effects of 19.75 years.

Mortality was estimated on the basis of a 10% mortality associated with gastric bleeds.[8] Estimates of mortality from gastric bleeds, in the published literature ranged from 4% to 14%. [8 9 10 11] Ten per cent was the most frequently quoted figure in the literature and was therefore used in the model. Rebleeds were calculated on the basis of 16% recurrence in the five years after original bleed. [6]

SENSITIVITY ANALYSIS

When modelling the outcome of clinical interventions, based on probabilities of events occurring, there is always a degree of uncertainty around the accuracy and precision of the probabilities used. In order to assess the generalisability of the results, additional analyses are often undertaken to identify the robustness of the results to changes in the key variables. This process, known as sensititivity analysis may take a number of forms,[12] including simple sensitivity analysis, where the values of key variables are varied over a plausible range; threshold analysis, where crucial values are changed to identify the point at which the conclusion of the study changes; and analysis of extremes, where a base case analysis using the best estimates of the true values for all the variables is accompanied by a version using the highest possible values for all variables and a further version using the lowest possible values for all variables.

For each NSAID, the NAB101 data provided a point estimate of the risk of any given side effect. A 95% confidence interval was calculated for each point estimate using the method described in Gardner and Altman.[13] Two models were then run, performing an analysis of extremes. The first replaced the point estimates of risk with the lower confidence limit values; the second replaced the point estimates of risk with the upper confidence limit values.

The highest and lowest expected costs of a gastric bleed were calculated using ECRs from units in Trent Region. These were used in the model to test the sensitivity of the outcomes to the cost of treating a major side effect.

RESULTS

The results are presented in four sections; first the results from the costing exercise, followed by the results for each of the decision tree models. The first decision tree model to be presented is the "Within Study" Treatment Decision Model, followed by the "Rational Practice" Treatment Decision Models with the three month time horizon model presented first, and the extended time horizon model presented second.

Costs

Cost of Three Months NSAID Treatment

The cost of each NSAID was calculated on the basis of NAB101 dosing, using price data from the Drug Tariff and the Chemist and Druggist Monthly Price Index (May 1995). The costs, representing a balanced combination of proprietary and generic costs, reflecting respective market share are as shown in Table 2

Table 2: Cost of Three Months Prescription for NSAIDs in Model

NSAID	Cost for 3 months Prescription (£s)
Nabumetone	68.45
Piroxicam	13.70
Naproxen	14.95
Ibuprofen	12.78
Diclofenac	37.77

Other Treatment Costs

The average expected cost of a gastric bleed was £1,964 for 1995/96. The lowest expected cost for a gastric bleed was £1,464 and the highest was £2,474. These prices include £150 for an emergency ambulance admission, and £303 for gastroenterology follow-up, including out-patients appointments. They also include the cost of general practitioner consultations pre-admission and post discharge.[14]

The cost of H2RA maintenance therapy for people who experienced PUBs was £179.00 for 55 weeks of treatment.

Within Study Model

The comparisons between Nabumetone and Ibuprofen, and Nabumetone and the Weighted NSAID combination, for the Within Study Model are summarised in Table 3. This table presents information on (i) the expected cost of three months treatment for each comparator, (ii) the additional cost of using Nabumetone rather than Ibuprofen or the Weighted NSAID combination, (iii) the cost per major side effect avoided by using Nabumetone rather than Ibuprofen or the Weighted NSAID combination, (iv) the cost per death avoided and (v) the cost per life year saved by using Nabumetone rather than Ibuprofen or the Weighted NSAID combination.

Table 3: Within Study Model: Results Summary

	Nabumetone	Ibuprofen	Weighted NSAID combination
Expected Cost per Patient (£s)	75.98 (74.10 to 80.05)	35.17 (16.99 to 85.11)	41.34 (27.05 to 85.10)
Incremental cost of Nabumetone (£s)	******	40.81 (-5.96 to +57.18)	34.64 (-4.94 to+ 47.04)
Cost per Major Side Effect Avoided using Nabumetone (£s)	******	4,971	6,097
Cost per Life Year Gained using Nabumetone (£s)	******	2,517	3,087
Cost per Death Avoided using Nabumetone (£s)	******	49,711	60,968

The total cost of treatment of a cohort of 20,000 patients receiving Nabumetone was £1,519,582. The model predicted 6 major side effects for this cohort of 20,000 patients and the expected mortality was 0.6 lives. Six thousand nine hundred and forty patients would experience minor side effects. Using the upper and lower confidence interval values established a total cost confidence interval representing a plausible range of costs from £1,482,047 to £1,603,176. The upper and lower estimates for the number of major side effects were 0 and 34 respectively, with an associated expected mortality of 0 and 3.4 lives.

The total cost of treatment of a cohort of 20,000 patients receiving Ibuprofen was £703,406. The model predicted 170 major side effects and the expected mortality was 17 lives. Five thousand six hundred and eighty patients would experience minor side effects. The lowest total cost estimate was £339,884, the highest was £1,722,303. The expected number of major side effects had a lower estimate of 20 and an upper estimate of 614, with associated mortality of 2 and 61.4 lives.

The total cost of treatment for a cohort of 20,000 patients receiving the Weighted NSAID combination was £826,851. The model predicted 114 major side effects and the expected mortality was 11.4 lives. Nine thousand three hundred and ninety patients would experience minor side effects. The confidence interval for total cost was £541,163 to £1,701,292. The lower estimate of major side effects was 11 and the upper estimate was 462. The associated mortality was 1.1 and 46.2 lives.

The expected cost per patient initiated on Nabumetone was £75.98 (confidence interval £74.10 to £80.16), an incremental cost over Ibuprofen of £40.81 (confidence interval -£5.96 to +£57.18). The expected cost per life year gained by prescribing

Nabumetone rather than Ibuprofen was £2,517 (confidence interval -£104 to +£28,346). The expected cost per life saved was £49,711.

The relative risk of minor side effects for Nabumetone and Ibuprofen is shown in Figure 3. This chart indicates the net incidence of side effects caused by using Nabumetone rather than Ibuprofen. Point estimates to the right of the chart indicates that Nabumetone causes a greater incidence of a particular side effect (i.e. favours Ibuprofen) whilst point estimates to the left indicate a reduction in incidence by using Nabumetone (i.e. favours Nabumetone). The horizontal bars indicate the 95% confidence intervals.

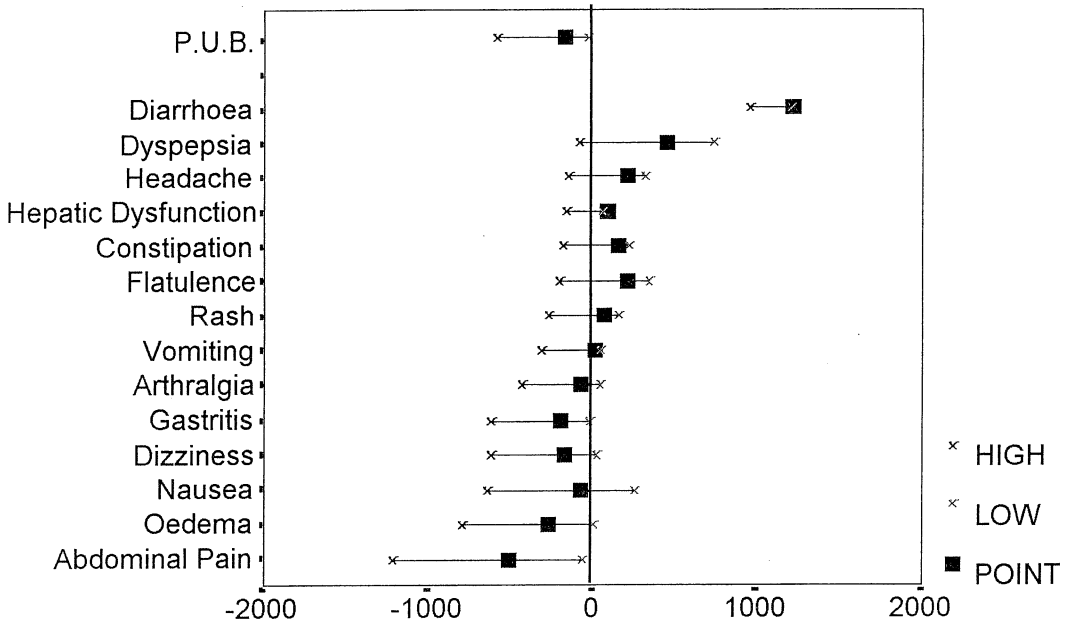
Figure 3 suggests a superior side effect profile for Nabumetone in terms of reduced incidence of minor side effects, although this is not unequivocal. The majority of the confidence intervals cross zero, indicating no statistical difference. Two minor side effects, gastritis and abdominal pain are statistically in favour of Nabumetone, and one, diarrhoea, is significantly favouring Ibuprofen. This is in addition to the statistically significant difference in PUB incidence that also favours Nabumetone.

The expected cost per patient initiated on the Weighted NSAID combination was £41.34 (confidence interval £27.58 to £85.10), giving an incremental cost for Nabumetone of £34.64 (confidence interval -£4.94 to +£47.04).

The cost per life year gained by using Nabumetone was £3,087 (confidence interval -£109 to +£41,106) . The cost per life saved was £60,968. Mapping the net incidence of side effects as described above (Figure 4) suggests that Nabumetone has a superior side effect profile. Twelve out of the fourteen point estimates for minor side effects lay to the left of the '0 point', favouring Nabumetone. Three of the

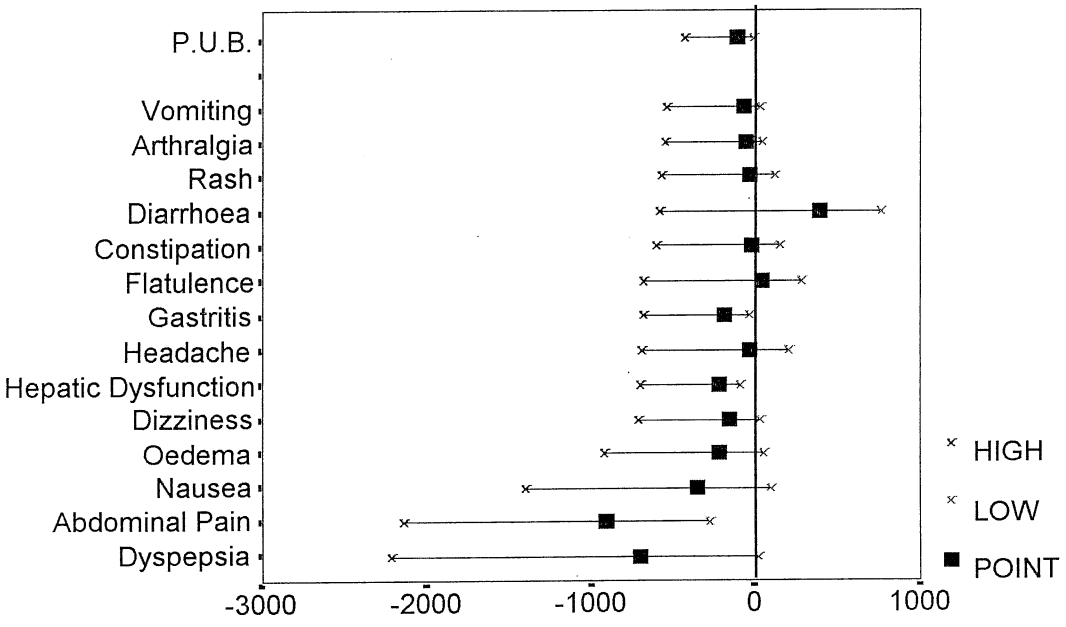
confidence intervals, Abdominal Pain, Gastritis and Hepatic Dysfunction, are completely to the left of the '0 point', indicating statistical significance.

Figure 3: Within Study Model Net Incidence of Side Effects in a Cohort of 20,000 Patients: Nabumetone vs Ibuprofen



Net Incidence of Side Effects per Cohort of 20,000 Patients

Figure 4: Within Study Model Net Incidence of Side Effects in a Cohort of 20,000 Patients: Nabumetone vs. Weighted NSAID Combination



Net Incidence of Side Effects per Cohort of 20,000 Patients

Rational Practice Model: Three Month Time Horizon

The comparisons between Nabumetone and Ibuprofen, and Nabumetone and the Weighted NSAID combination, for the Rational Practice Model 3 month time horizon are summarised in Table 4.

Table 4: Rational Practice Model; Three Month Time Horizon: Results Summary

	Nabumetone	Ibuprofen	Weighted NSAID combination
Expected Cost per Patient (£s)	63.14 (59.61 to 83.11)	37.54 (17.61 to 109.34)	40..43 (23.27 to 108.92)
Incremental Cost of using Nabumetone (£s)	******	25.60 (-26.23 to +42.00)	22.72 (-25.81 to +36.34)
Cost per Major Side Effect Avoided using Nabumetone (£s)	******	3,713	4,420
Cost per Life Year Gained using Nabumetone(£s)	******	1,880	2,238
Cost per Death Avoided using Nabumetone (£s)	******	37,130	44,201

The total cost of treatment for a cohort of 20,000 patients treated with Nabumetone was £1,262,847. The model predicted 48 major side effects and 4.8 lives lost as a result. Eight thousand nine hundred and sixty one patients would experience minor side effects. The confidence interval for costs, based on upper and lower 95% confidence limits indicating a plausible range of costs, was £1,192,246 to £1,662,168. The number of major side effects had a confidence interval from 3 to 243, and mortality had a confidence interval from 0.3 to 24.3 lives.

The total cost of treatment for a cohort of 20,000 patients treated with Ibuprofen was £750,899. The model predicted 186 major side effects and 18.6 lives lost. Seven

thousand six hundred and fifteen people would experience minor side effects. The lower estimate of total cost was £352,253, and the upper estimate was £2,186,721. The number of major side effects had a confidence interval from 21 to 816, and expected mortality had a confidence interval from 2.1 lives to 81.6 lives.

The total cost of treatment for a cohort of 20,000 patients on the Weighted NSAID combination was £808,526. The model predicted 163 major side effects and 16.3 lives lost. Eight thousand nine hundred and eighteen people would experience minor side effects. The confidence interval for total cost was £465,471 to £2,178,404. Expected number of major side effects had a confidence interval from 16 to 779, and mortality had a confidence interval from 1.6 lives to 77.9 lives.

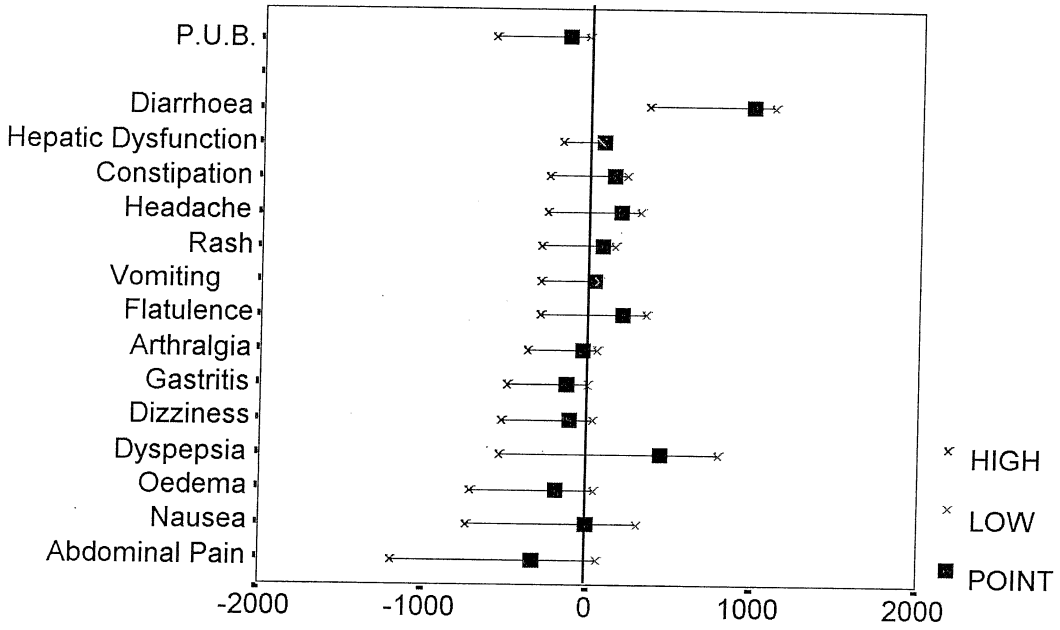
The expected cost for a patient initiated on Nabumetone was £63.14 (confidence interval £59.61 to £83.11). The incremental cost over Ibuprofen was £25.60 (confidence interval -£26.23 to +£42.00). The expected cost per life year gained by prescribing Nabumetone rather than Ibuprofen was £1,881 (confidence interval -£463 to +£24,566). The expected cost per life saved was £37,149.

PUBs are significantly less frequent with Nabumetone than either Ibuprofen or the Weighted NSAID combination. With regard to minor side effects almost all the confidence intervals cross zero (Figure 5). The only exception to this is gastritis which is less common amongst the Nabumetone cohort than the Ibuprofen cohort over the whole confidence interval, and diarrhoea, which is more common amongst the Nabumetone cohort over the whole confidence interval. The balance of clinical advantage appears to lie with Nabumetone.

The expected cost for a patient initiated on the Weighted NSAID combination was £40.43 (confidence interval £23.27 to £108.92). The incremental cost for Nabumetone was £22.72 (confidence interval -£25.81 to + £36.64). The expected cost per life year gained by using Nabumetone was £2,238 (confidence interval -£507 to +£37,698). The expected cost per life saved was £44,201.

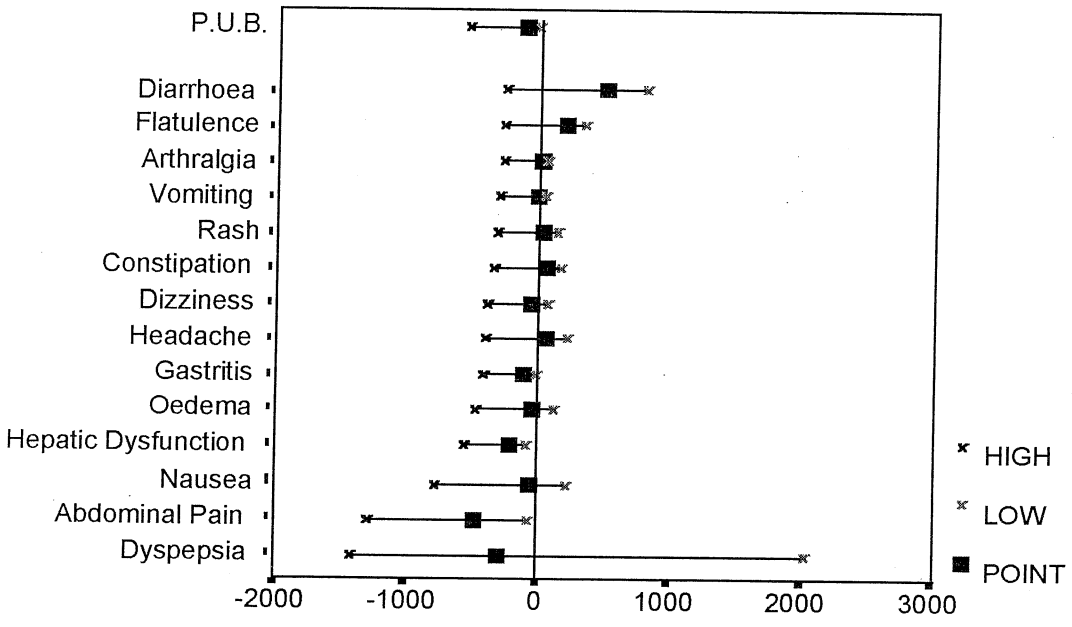
Whilst the confidence intervals for almost all of the minor side effects cross zero, abdominal pain is less common amongst the Nabumetone cohort across the confidence interval as are hepatic dysfunction and gastritis. (Figure 6)

Figure 5: Rational Practice Model Net Incidence of Side Effects in a cohort of 20,000 patients: Nabumetone Vs Ibuprofen



Net Incidence of Side Effects per Cohort of 20,000 Patients

Figure 6: Rational Practice Model Net Incidence of Side Effects in a cohort of 20,000 patients: Nabumetone vs. Weighted NSAID Combination



Net Incidence of Side Effects per Cohort of 20,000 Patients

Rational Practice Model: Extended Time Horizon

The comparisons between Nabumetone and Ibuprofen, and Nabumetone and the Weighted NSAID combination, for the Rational Practice Model: extended time horizon are summarised in Table 5.

Table 5: Rational Practice Model Extended Time Horizon: Results Summary

	Nabumetone	Ibuprofen	Weighted NSAID combination
Expected Cost per Patient (£s)	64.20 (59.68 to 88.49)	41.67 (18.07 to 127.44)	44.04 (23.62 to 126.19)
Incremental Cost of using Nabumetone (£s)	******	21.21 (-38.95 to +41.62)	19.06 (-37.70 to +36.06)
Cost per Major Side Effect Avoided using Nabumetone (£s)	******	3,271	3,924
Cost per LifeYear Gained using Nabumetone(£s)	******	1,656	1,987
Cost per Death Avoided using Nabumetone (£s)	******	32,706	39,243

The total cost of treatment for a cohort of 20,000 patients treated with Nabumetone was £1,284,114. The model predicted 48 major side effects and 4.8 lives lost as a result. The confidence interval for costs, based on upper and lower 95% confidence limits, representing a plausible range of costs, was £1,193,728 to £1,769,830. The number of major side effects had a confidence interval from 3 to 243, and mortality had a confidence interval from 0.3 to 24.3 lives.

The total cost of treatment for a cohort of 20,000 patients treated with Ibuprofen was £833,314. The model predicted 186 major side effects and 18.6 lives lost. The lower estimate of total cost was £361,416 and the upper estimate was £2,548,804. The

number of major side effects had a confidence interval from 21 to 816, and expected mortality had a confidence interval from 2.1 lives to 81.6 lives.

The total cost of treatment for a cohort of 20,000 patients on the Weighted NSAID combination was £880,799. The model predicted 163 major side effects and 16.3 lives lost. The confidence interval for total cost was £472,437 to £2,523,866. Expected number of major side effects had a confidence interval from 16 to 779, and mortality had a confidence interval from 1.6 lives to 77.9 lives.

The expected cost for patients initiated on Nabumetone was £64.20 (confidence interval £59.69 to £88.49). The incremental cost over Ibuprofen was £22.21 (confidence interval -£38.95 to +£41.62). The expected cost per life year gained by prescribing Nabumetone rather than Ibuprofen was £1,656 (confidence interval -£688 to +£24,342). The expected cost per life saved was £32,706.

The expected cost for patients initiated on the Weighted NSAID combination was £44.04 (confidence interval £23.62 to £126.19), giving an incremental cost for Nabumetone of £20.16 (confidence interval-£37.70 to +£36.06). The expected cost per life year gained by using Nabumetone was £1,987 (confidence interval -£740 to +£37,414). The expected cost per life saved was £39,243.

DISCUSSION

The Model

The models presented in this paper are by definition a simplification of reality. Three key simplifications are worthy of further consideration; first the choice of comparators, secondly the adoption of a 'rational prescribing' decision rule, and thirdly the choice of study population. There is a further issue relating to the dose of Ibuprofen.

Choice of comparators

Ibuprofen is an obvious choice as a comparator to Nabumetone given that it is a commonly prescribed NSAID in the UK, and is the least costly in terms of acquisition cost of the NSAIDs evaluated in the NAB101 study. This said, it is often prescribed for pain relief rather than for its anti-inflammatory effects. In the treatment of OA and RA, Diclofenac may be considered by some as a more relevant comparator. A separate comparison was therefore carried out and found that Nabumetone saved life years when compared with Diclofenac at a cost per life year comparable to services presently available from the NHS. The cost per life year saved by using Nabumetone was £3,786 in the Within Study Model, and £2,290 in the Rational Practice 3 month model.

Rational Practice Decision Rule

The Rational Practice Models assume that doctors act rationally when prescribing NSAIDs (i.e. they consciously or unconsciously follow a specific guideline or set of prescribing rules when deciding on an appropriate treatment). Given the resources that have been spent on research on improving the rationality of doctors prescribing, this may be a big assumption. A version of the model in which the second line

NSAID is determined by market share, as a proxy for observed behaviour, has been constructed. The relative costs and outcomes of Nabumetone and the alternative NSAIDs obtained from the market share model were very similar to those obtained from the rational practice model. The expected cost of treatment using Nabumetone was only 2.3% higher in the market share model than the Rational Practice Model. The expected cost of treatment using Ibuprofen was 2.2% lower in the market share model than the Rational Practice Model.

Choice of study population

The NAB101 study evaluated the outcomes for OA and RA as a single group[1]. Whilst it might also be considered appropriate to evaluate the two patient groups separately the structure of the sample was such that separate analyses of major side effects would not have had acceptable statistical power. Therefore, the economic evaluation has modelled the costs and outcomes for the two groups together.

Dosage of Ibuprofen

The dose range for Ibuprofen, used in the NAB101 study included higher doses than are approved in the United Kingdom. However, the doses actually prescribed in the NAB101 study were almost all within the recommended range for the UK. Only 10% of patients received dosages of either 2800mg or 3200mg, as indicated by the dose at end of study.[5]

The use of the Iboprofen dosages above 1200mg by the majority of patients (57%)[5] is concordant with the view of the original manufacturers of Ibuprofen. Busson[15] indicates that dosages of 1200mg to 1800mg give better therapeutic control than

lower dosages (600mg to 800mg) and that dosages of up to 2400mg may be necessary to control severe inflammatory symptoms.[15]

It is also worth noting that the dose of Ibuprofen prescribed to those patients who experienced perforations, ulcers and bleeds (PUBs) was 1200mg, well within the recommended dose range for the UK.[1]

Economic Evaluation

The constraining pressures that have been brought to bear on prescribing costs in both the primary and secondary sectors of the health service mean that cost has been added to efficacy and safety as a primary consideration in the prescribing process. It is important that cost considerations are not limited to the price of prescribing any specific drug, especially where side effects are a significant issue.

When considering cost containment in the prescribing budget, at practice, trust or service level, NSAIDs are always likely to be considered, if for no other reason than the volume of prescriptions written for these products. The range of prices for NSAIDs is remarkably large and prescription cost savings that might be made by substituting cheaper NSAIDs prescriptions for those that cost more appear to be significant. However, NSAIDs are known to have significant side effects, some of which can be life threatening and expensive to treat e.g. peptic ulcers and bleeds. Therefore, any evaluation of alternative NSAIDs must take account of the costs that the system will bear in treating side effects. Savings in the prescribing budget may be at least potentially offset by additional costs incurred by different parts of the NHS, such as the surgery or gastroenterology budget. This paper presents an evaluation which incorporates the costs of managing side effects into the economic evaluation of alternative NSAIDs. In addition, it has allowed for the fact that side

effects are undesirable events in themselves, separate from the costs incurred in their management and has compared the relative incidence of these side effects between Nabumetone and alternative NSAIDs.

CONCLUSION

A number of points have emerged from the analysis:

1. The major side effects profile (gastric bleeds) unequivocally favours Nabumetone against both comparators

2. The minor side effects profile appears to favour Nabumetone against both Ibuprofen alone and "other NSAID's".

3. Using point estimates for the risk of side effects, Nabumetone is more expensive than either Ibuprofen alone or a weighted combination of "other NSAIDS" for each model considered even when the cost of treating side effects is taken into account. However, use of Nabumetone rather than the alternatives will reduce the incidence of gastric bleeds which are associated with a finite mortality. This means that lives and life years can potentially be saved by using Nabumetone. Point estimates of cost/life year gained by using Nabumetone rather that the alternatives range from £1,656 to £3,087 depending on the model used. These figures compare favourably with other expenditures used to lower mortality within the NHS. For patients who face a greater than average risk of major side effects, the cost per life year gained by using Nabumetone will be still lower. Some comparator costs are shown in Table 6.

Table 6: Published Cost per Life Year Valuations for Selected Interventions[16]

Intervention	Cost per Life Year (£s 1991)
Treatment of severely injured victims in specialist trauma centres	853
Opportunistic Lipid Screening in General Practice	3671
Nicotine gum to physician advice against cigarette smoking in primary care: Men aged 35-39	3934
Coronary Care unit provision for people experiencing myocardial infarction	4974
Breast Cancer Screening for Women aged 45 to 65	8,417
Formal Screening for cervical cancer	9,070
Intensive Care Treatment for Patients with multiple trauma	9,977
Use of Neonatal Intensive Care Unit: Birth Weight 500 to 999g	11,400
Kidney Transplant with Immunosuppressive Therapy	17,400
Haemodialysis	27,000

4. The construction of two decision tree models has shown how differences in the management of side effects can lead to considerable differences in the total cost of treatment and the incidence of side effects. There are issues around the management of minor side effects, and possible interactions between compliance, cost and efficacy of treatment which need to be examined and may be the basis of further research.

5. The sensitivity analysis has not identified any scenarios where Nabumetone was unequivocally superior or inferior, in economic terms, to the alternative NSAIDs. Choice should therefore depend upon the importance attached to specific side effects. If reducing the risk of major side effects is a priority then the additional potential cost of prescribing Nabumetone to achieve this end compares favourably to many expenditures already made within the NHS.

(Table 6). On this basis, use of Nabumetone may be considered a cost-effective use of resources from a health service perspective.

6. The research has identified a number of limitations of available ecconomic data to assist with choices between NSAIDs. Ideally, a prospective, randomised, naturalistic economic trial would be conducted. This would need to include, inter alia, an assesment of how the differences in side effects affects quality of life outcomes. However, the potential size of such a trial is likely to present a barrier to its conduct.

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